Original Article

Efficacy and Safety of Fondaparinux Versus Enoxaparin in The Management of Unstable Angina and NSTEMI

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Abstract:

Background: Unstable angina (UA) and Non-ST elevation myocardial infarction (NSTEMI) impose significant health and economic burden on Bangladesh. Anticoagulants are recommended as standard therapy by various clinical practice guidelines. Recent studies have shown fondaparinux's superiority over enoxaparin in patients with UA & NSTEMI, especially in bleeding reduction. The description of this finding has not yet been documented in any study from Bangladesh. This study aimed to evaluate the efficacy and safety of fondaparinux compared with enoxaparin in the management of UA & NSTEMI.

Methods: This prospective observational study included 177 patients (fondaparinux=87, enoxaparin=90) with UA and NSTEMI admitted to the Department of Cardiology of Abdul Malek Ukil Medical College Hospital, Noakhali, Bangladesh. The primary outcome was to determine whether fondaparinux was non-inferior to enoxaparin in preventing the composite of death, new myocardial infarction, and refractory ischemia, readmission in the hospital for heart failure within six months after anticoagulant therapy. The primary safety outcome was to evaluate the rates of major bleeds in the two groups.

Results: The minor (6.9% versus 20%, p=0.002) and major (0% versus 3.3%, p=0.002) bleeding events were less frequently observed with Fondaparinux than enoxaparin. Myocardial ischemia (3.4% vs. 14.4%, p=0.011) and recurrent ischemia (11.5% vs. 24.4%, p=0.025) were less frequent in Fondaparinux than in the enoxaparin group. Fondaparinux was associated with a reduced number of deaths in 3 months (6.2% vs. 12.5%) and 6 months (5.1% vs. 13.3%) without any statistical significance (p>0.05). In the fondaparinux group, 20.7% of patients experienced a composite event within 6 months, compared with 40% of patients in the enoxaparin group (OR:0.659, 95% CI 0.500-0.867, p=0.005).

Conclusion: Similarly, to recently published data in international literature, fondaparinux proved superior to enoxaparin for the Bangladeshi population, with a significant reduction of combined events and bleeding in patients with UA & NSTEMI.

Keywords: *Unstable Angina; NSTEMI; Enoxaparin; Fondaparinux; Hemorrhage; Mortality; Morbidity.*

(Bangladesh Heart Journal 2024; 39(1): 31-37)

Introduction:

Coronary artery disease (CAD) is a leading cause of death worldwide and the global prevalence of IHD is rising. Moreover, health systems have to manage an increasing number of cases due to population aging.[1] In

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DOI: https://doi.org/10.3329/bhj.v39i1.70709

a recent meta-analysis a high CAD prevalence along with an upward trend was observed in Bangladeshi adults. So, it can be assumed that CAD is a major health issue and represents a significant economic burden for Bangladesh.[2] From our practical experiences it has been observed that there is a rising trend of hospitalization due to CAD in both public and private hospitals in Bangladesh. Actually, CADs are growing by epidemic proportions day by day in Bangladesh.[3]

Acute coronary syndrome (ACS) is a spectrum of life-threatening CADs usually due to coronary artery plaque rupture, with subsequent thrombin generation, platelet activation, and thrombus formation.[4] Patients present either with typical acute chest pain and persistent (>20 min) ST-segment elevation on ECG, which is usually indicative of acute total occlusion, or more commonly (and the population discussed in this review), with acute chest pain without persistent ST-segment elevation, which is usually indicative of partial or intermittent occlusion.[4,5]

Once a diagnosis of NSTE-ACS (UA & NSTEMI) is likely or definite, anti-ischemic drugs are introduced as indicated, including beta-adrenoceptor antagonists and angiotensin II receptor antagonists. A management strategy is then decided based on the level of risk.[5] Current treatment guidelines for patients with NSTE-ACS generally recommend an invasive strategy (i.e., diagnostic angiography followed by possible percutaneous and/or surgical revascularization) for average- to high-risk patients or a conservative management approach (i.e., a selectively invasive strategy) for those with lower risk scores.[5,6]

Pharmacological recommendations and sequence of therapy will depend on the individual hospital's management strategy and treatment guidelines, but, for both invasive and conservative strategies, a combination of antiplatelet and anticoagulation agents is recommended.[5] Most commonly, antiplatelet therapy will comprise aspirin plus clopidogrel and/or a glycoprotein IIb/ IIIa (GP) inhibitor, followed by an anticoagulation agent. Options for anticoagulation therapy include unfractionated heparin (UFH), bivalirudin, and low-molecular-weight heparins, such as enoxaparin, and fondaparinux.[4,5]

Fondaparinux is a well-established synthetic anticoagulant that inhibits thrombus formation by interrupting the blood coagulation cascade through antithrombin III-mediated selective inhibition of factor Xa.[6,7] The Fifth Organization to Assess Strategies in Ischemic Syndromes (OASIS 5) trial showed fondaparinux to reduce the rate of major bleeding and net clinical benefit including death, Myocardial Infarction (MI), stroke, and major bleeding in comparison to enoxaparin.[8,9] However, results from the French Registry of ST-segment elevation and non-ST segment elevation MI (NSTEMI) 2010 showed a similar rate of bleeding and mortality between fondaparinux and enoxaparin.[10] On the other hand different registry-based data provided evidence in favor of fondaparinux compared to enoxaparin in terms of cost effectivity and efficacy. [11-22]

Though data from different settings are increasingly available in the literature regarding the comparative benefit of fondaparinux over enoxaparin in cases of NSTE-ACS, this issue is rarely addressed in Bangladesh. In this background, this study is designed to compare fondaparinux to enoxaparin in in-hospital prognosis and short-term outcome of NSTE-ACS in a group of Bangladeshi population.

Methods:

A prospective observational study was conducted in the Department of Cardiology, Abdul Malek Ukil Medical College & Hospital, Noakhali, Bangladesh from January 2022 to December 2022. Prior approval was obtained from the Ethical and Review Committee of Abdul Malek Ukil Medical College and permission for data collection was obtained from the hospital administrator. Prior to inclusion in the study, written informed consent was obtained from the study participants after the study purpose and procedures were explained to them.

Consecutively Admitted patients with a diagnosis of Unstable Angina and NSTEMI were included. Patients were excluded if they had contraindications to LMWH, recent hemorrhagic stroke, indications for anticoagulation other than an ACS, have a serum creatinine level of at least 3 mg per deciliter, patients with STE-ACS, pregnancy, and comorbid conditions with life expectancy <6 months. Finally, it was possible to include 177 patients in the study within the limited time and resources.

The primary efficacy parameters are preventing death, MI, or refractory ischemia in the acute treatment of patients with Unstable Angina and NSTEMI. The primary safety objective is to evaluate whether fondaparinux is superior to enoxaparin in reducing major bleeding. Obesity was defined as BMI e" 27.5 kg/m^2.[22] Dyslipidemia: Diagnosed by NCEP: ATP-III criteria:[23] Major or minor bleeding was defined using the BARC score types 3 and 5, and minor bleeding using types 1 and 2.[24]

From the eligible participants the following data were obtained: age, gender, presence of diabetes mellitus, systemic arterial hypertension, smoking habit, dyslipidemia, family history of early onset coronary disease, previous coronary artery disease (previous angioplasty or coronary artery bypass surgery), hemoglobin, creatinine, peak troponin, Killip classification, left ventricle ejection fraction, medications used in the first 24 hours of hospital admission and adopted coronary treatment. Eligible patients received either fondaparinux 2.5 mg once daily by subcutaneous injection or enoxaparin (1 mg/kg) twice daily by subcutaneous injection. If creatinine clearance is <30 mL/min, the enoxaparin dosage was reduced to 1 mg/kg once daily. Fondaparinux was given for a mean of 6 days or hospital discharge (whichever was earlier), and enoxaparin was given for 2 to 8 days or until clinically stable as per its current approval for use in UA and NSTEMI. The minimum duration of therapy was 2 days; however, catheterization and PCI can be scheduled earlier than this time if necessary.

Outcome assessment: Patients were followed up regularly during their hospital stay for the outcome assessment. After discharge, they were asked to attend follow-up monthly for six months. Moreover, they were requested to inform the research assistant if there were any adverse events.

Data were expressed as frequency and proportion for the qualitative variables and mean (standard deviation) or Median (interquartile range) for the continuous variables. The analyses include all patients who underwent randomization. Comparisons between groups were done using the Chi-Square test for categorical variables. For continuous variables, when data showed normal distribution, the t-test was used, with significance considered at $p < 0.05$. When the distribution did not follow the normality pattern, we used the Mann-Whitney U test. P value < 0.05 was considered to represent a statistically significant difference. All calculations were made using the SPSS 23.0 statistical.

Results:

The mean age was around 60 years and there was male preponderance in both groups, 61 years old, and approximately 63% of participants were male. The most prevalent risk factor was systemic arterial hypertension, followed by smoking, diabetes Mellitus, and dyslipidemia. The majority of the patients in both groups were in Killip class-I. Overall, 100% of patients in the fondaparinux group and 98.9% in the enoxaparin group received aspirin, 51.7% and 53.3% received ACE inhibitors, and 56.3% and 50% received Beta blockers, respectively. Table 1 shows that both groups were similar in terms of their baseline clinical and biochemical characteristics.

Table-I

Baseline demographic and clinical characteristics between two groups

Variables	Fondaparinux (n=87)	Enoxaparin (n=90)	P value
Age, years	60.2±8.3	60.1±10.7	0.928†
Sex			
Male	62 (71.3)	75 (83.3)	0.055*
Female	25 (28.7)	15 (16.7)	
Interval from symptom onset to injection, hours	7.3 ± 2.0	7.3 ± 3.5	0.915†
Risk factors			
Hypertension	57 (65.5)	54 (60.0)	0.448*
Smoking	57 (65.5)	67 (74.4)	0.195*
Obesity	7 (8.0)	2 (2.2)	0.078‡
Dyslipidemia	38 (43.7)	42 (46.7)	0.690*
Diabetes mellitus	37 (42.5)	37 (41.1)	0.848*
H/O CAD	21 (24.1)	22 (24.4)	0.962*
H/O stroke	7 (8.0)	7 (7.8)	0.947*
H/O ACS	19 (21.8)	26 (28.9)	0.282*
H/O PCI	5 (5.7)	2 (2.2)	0.229
H/O CABG	1 (1.1)	1 (1.1)	0.998*
Examination findings			
Heart rate, /min	75.7±12.9	76.5±11.5	0.633†
SBP, mmHg	118.5±13.3	119.8±20.6	0.628†
DBP, mmHg	75.5±10.8	75.7±14.4	0.938†
Killip classification			
Class I	70 (80.5)	69 (76.7)	0.539*
Class II	17 (19.5)	21 (23.3)	
Ejection fraction, %	55.2±6.6	54.5±9.5	0.5588†
Medication received			
Aspirin	87 (100.0)	89 (98.9)	0.998‡
Clopidogrel	87 (100.0)	90 (100.0)	NA
ACE inhibitor	45 (51.7)	48 (53.3)	0.830*
Beta-blocker	49 (56.3)	45 (50.0)	0.339*
CCB	2 (2.3)	4 (4.4)	0.680‡
Anti lipid	85 (97.7)	86 (65.6)	0.430‡
Biochemical parameters			
Hemoglobin, g/dl	11.4±1.1	11.6±1.5	0.209†
S. Creatinine, mg/dl	1.3±0.4	1.2±0.4	0.545†
RBS, mmol/L	8.3±3.0	8.6±3.5	0.565†

Data were expressed as frequency (%) or mean ±SD; CAD: Coronary artery disease; ACS: Acute coronary syndrome; PCI: Primary coronary intervention; CABG: Coronary artery bypass graft; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CCB: Calcium channel blocker; RBS: Random blood sugar. *Chi-square test; †Unpaired t test; ‡Fisher's exact test.

Comparatively fewer patients had recurrent ischemia and in-hospital mortality in the fondaparinux group than in the enoxaparin group without any statistical significance (Table II) during their initial hospital stay. At 3-month follow-up, there was a trend toward a lower rate of death,

myocardial infarction, or refractory ischemia with fondaparinux than with enoxaparin without any statical significance. At the 6-month follow-up, there was a trend of a lower rate of death reaching statistical significance in fondaparinux than in enoxaparin. The rate of minor bleeding during hospital stay was substantially down in the fondaparinux group than in the enoxaparin group (17.8% vs 4.6%). However, this difference did not persist during 3 and 6- months of follow-ups. Very few patients had major or minor bleeding after discharge from the hospital. No significant difference was observed between the two groups regarding major or minor bleeding at 3-month and 6-month follow-ups (Table II).

Table-II
Outcome parameters between two groups up to 6 months

Variables	Fondaparinux (n=87)	Enoxaparin (n=90)	P value
In-hospital outcome			
Mortality	0 (0)	2 (2.2)	0.497‡
Minor bleeding	4 (4.6)	16 (17.8)	0.005*
Major bleeding	0 (0)	1 (1.1)	1.0‡
Recurrent ischemia	8 (9.2)	16 (17.8)	0.095*
Heart failure	17 (19.5)	21 (23.3)	0.539*
3-months outcome	(n=87)	(n=88)	
Mortality	8 (6.2)	11 (12.5)	0.360*
Minor bleeding	1 (1.1)	1 (1.1)	1.0‡
Major bleeding	0 (0)	2 (2.2)	1.0‡
Myocardial infarction	2 (2.3)	4 (4.4)	0.682‡
Recurrent ischemia	2 (2.3)	8 (8.9)	0.058‡
Stroke	1 (1.1)	3 (3.3)	0.621‡
Hospitalization for HF	1 (1.1)	3 (3.3)	0.444‡
Heart failure	7 (8.0)	14 (16.9)	0.109*
6-months outcome	(n=79)	(n=75)	
Mortality	4 (5.1)	10 (13.3)	0.074*
Minor bleeding	1 (1.3)	1 (1.3)	1.0‡
Myocardial infarction	1 (1.3)	9 (12.0)	0.008‡
Recurrent ischemia	1 (1.3)	2 (2.7)	0.480‡
Stroke	0 (0)	1 (1.3)	0.487‡
Hospitalization for HF	2 (2.5)	8 (10.7)	0.052‡
Revascularization	0 (0)	3 (4.0)	0.115‡
Heart failure	13 (16.5)	21 (28.0)	0.084*

Data were expressed as frequency (%); HF: Heart failure; *Chi-square test; ‡Fisher's exact test.

Overall, during the 6-month follow-up period, there were significant differences in recurrent ischemia, stroke, and hospitalization requirement for heart failure between the fondaparinux and enoxaparin group, with a lower risk of these events in the fondaparinux group than the enoxaparin group (Table III). The minor and major bleeding events were less frequently observed with Fondaparinux than with enoxaparin. Still, only the difference in minor bleeding rate between the two groups reached statistical significance (6.9% versus 20%, p=0.002) (Table III).

Table-III
Comparison of 6 months outcome between two groups

Variables	Fondaparinux (n=87)	Enoxaparin (n=90)	P value
Mortality	12 (13.8)	23 (25.6)	0.049*
Minor bleeding	6 (6.9)	18 (20.0)	0.002*
Major bleeding	0 (0)	3 (3.3)	0.416‡
Myocardial infarction	3 (3.4)	13 (14.4)	0.011*
Recurrent ischemia	10 (11.5)	22 (24.4)	0.025*
Stroke	1 (1.1)	4 (4.4)	0.368‡
Hospitalization for HF	4 (4.6)	13 (14.4)	0.026‡
Revascularization	0 (0)	3 (3.3)	0.246‡
Heart failure	25 (28.7)	32 (35.6)	0.322

Data were expressed as frequency (%); HF: Heart failure; *Chi-square test; ‡Fisher's exact test

In the fondaparinux group, 20.7% of patients experienced a hospital admission for heart failure, death, MI, recurrent ischemia, or stroke within 6-months, compared with 40.0% of patients in the enoxaparin group, which indicated that the fondaparinux was associated with lower risk of the composite outcome of those events (OR:0.659, 95% CI 0.500-0.867, p=0.005) than the enoxaparin (Table IV).

Table-IV
Comparison of composite efficacy parameters between two groups

Any of the adverse cardiovascular event	Fondaparinux (n=87)	Enoxaparin (n=90)	OR (95%CI)	P value
No	69 (79.3)	54 (60.0)	0.659	0.005
Yes	18 (20.7)	36 (40.0)	(0.500-0.867)	

Data were expressed as frequency (%); OR: Odds ratio; CI: Confidence interval; *Chi-square test.

Discussion:

The present study showed important data reproduced in the Bangladeshi population that are in line with results from recent publications from literature.[14] The present study has three important findings. First, in the short term, fondaparinux and enoxaparin have similar efficacy. Second, as compared with enoxaparin, fondaparinux substantially reduces bleeding. Third, the reduced bleeding that accompanies the use of fondaparinux is associated with lower long-term mortality and morbidity. The present study findings were in line with a recent meta-analysis where the authors concluded in patients who were treated for ACS, fondaparinux might be a better choice when compared to enoxaparin in terms of short to midterm bleeding events.[25]

Fondaparinux was statistically superior to enoxaparin with respect to the primary composite outcome of death, myocardial infarction, or refractory ischemia at 6 months. Analysis of the rates of each component of the composite outcome, including death or myocardial infarction, yielded similar results. In the present study, major bleeding events were few, and no event was detected in the fondaparinux group and only three events in the enoxaparin group. However, minor bleeding events were significantly less in fondaparinux than in enoxaparin.

Bleeding increased the long-term risk of death,[26,] and differences in bleeding appeared to account for the reduction in the long-term risk of death with fondaparinux. In addition, there were significantly fewer strokes with fondaparinux than with enoxaparin. Therefore, the net clinical benefit is clearly in favor of fondaparinux. The reduction in bleeding was consistently observed for episodes that were fatal, serious, or minor. Several previous studies have found increased rates of death, stroke, and myocardial infarction among persons who had a bleeding episode.[26,27]

Lastly, due to bleeding reduction and the consequent smaller rate of mortality and events stemming from fondaparinux use, several studies have shown better cost-benefit of its use in relation to enoxaparin.[22,28-30] An OASIS-5 study sub-analysis showed, after 180 days, an average cost reduction of up to 547 dollars per patient in the group that used fondaparinux, highlighting the medication's superiority even further.[22]

In Bangladesh, hospital-based data have shown that the prevalence of ACS is quite varied, and the time taken to reach the hospital after symptom onset is more than in the Western world and it is an area of concern. Hence, a patient who is presented later than 6 h (i.e., has been suffering for an extended period) especially needs prompt and effective treatment. Effective antithrombotic treatment in the form of antiplatelet agents and anticoagulants has been accepted as the cornerstone of therapy for ACS. However, reducing ischemic events without increasing bleeding risk with matchless anticoagulant therapy is the need of the hour. This requirement is remarkably fulfilled by the novel anticoagulant Fondaparinux, with its unique mode of action, once-daily administration, efficacy across patient groups, and consistent effectiveness in reducing bleeding risk.

Limitations:

There are some limitations in this study. This was a single-center-based study with a small sample size. The non-randomized observational design was another major limitation.

Conclusions:

Similarly, to the recently published data in international literature, fondaparinux was proved superior to enoxaparin when administered in Bangladeshi patients with unstable angina and NSTEMI, with a significant reduction of combined events and bleeding. Fondaparinux at a dose of 2.5 mg daily is superior to enoxaparin in the short term in preventing ischemic events among patients with ACS without STEMI, and it is associated with substantially less bleeding — an effect that translates into lower long-term mortality and morbidity.

Recommendations:

Fondaparinux is an attractive option as an anticoagulant in the short-term care of patients with UA and NSTEMI. However, a large-scale multicenter randomized controlled trial is necessary to validate the current findings in the Bangladeshi population.

Acknowledgment:

The authors are grateful to Chittagong Medical University (CMU) as this publication was supported by a research grant from CMU. The authors would like to acknowledge the support of the healthcare professionals of the Cardiology Department of Abdul Malek Ukil Medical College & Hospital, Noakhali, Bangladesh.

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